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Attorney Docket: 27493U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Ranga NAMBURI et al.	Confirmation No.: 2736
Serial No.: 10/617,350	Art Unit: 1614
Filed: July 11, 2003	Examiner: ANDERSON, J.

For: **ORAL DOSAGE FORMS OF WATER INSOLUBLE DRUGS AND METHODS OF MAKING THE SAME**

APPEAL BRIEF

This is an appeal to the Board of Patent Appeals and Interferences from the decision of Examiner James D. ANDERSON, mailed June 12, 2009, twice rejecting claims 1-7, 15-20, 22-23, and 42. Appellant filed a Notice of Appeal on December 10, 2009, making this Appeal Brief due by February 10, 2010. A Petition for a Four-Month Extension of Time is submitted herewith, extending the period for filing this Appeal Brief to June 10, 2010. Accordingly, this paper is timely filed.

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2. The Real Party in Interest

The real party in interest in this appeal is the assignee, Stiefel Laboratories, Inc.

3. Related Appeals and Interferences

Appellants are not aware of any other appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

4. Status of Claims

The status of the claims is as follows upon filing of this Appeal Brief:

Claims cancelled: 8, 14, and 21

Claims withdrawn from consideration but not cancelled: 9-13 and 24-41

Claims pending: 1-7, 15-20, 22-23, and 42

Claims objected to: None

Claims allowed: None

Claims rejected: 1-7, 15-20, 22-23, and 42

The claims on appeal are 1-7, 15-20, 22-23, and 42.

5. Status of Amendments

All previously submitted amendments to the claims have been entered into the record. As such, Appellants submit that claims 1-7, 15-20, 22-23, and 42 are the currently pending claims of record. The claims listed in the claims appendix herein list all of the presently pending claims as currently amended.

6. Summary of Claimed Subject Matter

The presently claimed subject matter relates to a novel, unobvious method for manufacturing a water-insoluble azole antifungal active agent oral dosage form, and a particle produced thereby.

In particular, pending independent claim 1 claims a method of manufacturing a water-insoluble azole antifungal active agent oral dosage form, said method comprising the steps of: providing a single phase working solution comprising a water-insoluble azole antifungal active agent, water, a water-soluble polymer and a solvent, said solvent selected from the group consisting of alcohol, acetone, and mixtures thereof; providing core particles formed from a pharmaceutically acceptable material; combining said working solution with said particles to produce water-insoluble azole antifungal active agent-coated particles; drying said water-insoluble azole antifungal active agent-coated particles; and forming said dried particles into an oral dosage form; wherein said working solution is essentially free of methylene chloride, and said oral dosage form is essentially free of methylene chloride.

Similarly, claim 23 claims a pharmaceutically acceptable particle produced by the process of claim 1.

All other currently pending claims under prosecution are dependent, directly or indirectly, from claim 1.

7. Grounds of Rejection to be Reviewed on Appeal

A. Rejection of claim 23 under 35 U.S.C. §§ 102(b) or 103(a)

Whether the identified claim is unpatentable under 35 U.S.C. §§ 102(b) or 103(a) as being anticipated by, or in the alternative, obvious over Gilis et al. (WO 00/03697). The Examiner asserts that Gilis et al. teach pharmaceutically acceptably particles comprising a water-insoluble azole antifungal agent and a water-soluble polymer coated onto core particles. Further, the Examiner asserts that Gilis et al. teach a residual dichloromethane content of less than 600 ppm, preferably less than 250 ppm. Accordingly, the Examiner indicates that the patentability of the present product by process claim is dependent on the product itself, and the cited reference meets the claimed requirement of "said oral dosage form is essentially free of methylene chloride."

B. Rejection of claims 1-6, 15-16, 18-20, 22-23, and 42 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as being unpatentable over Gilis et al. and Ishibashi et al. (U.S. Patent Application Publication No. 2003/0012815) in view of Lynenskjold et al. (U.S. Patent Application Publication No. 2003/0211168) and Nara et al. (U.S. Patent No. 6,245,351). According to the Examiner, Gilis et al. clearly suggests a process of forming drug-coated particles comprising the same steps as those instantly claimed, while differing from the present claims "**only** with respect to the solvent used in the coating solution." The Examiner indicates that Gilis et al. use methylene chloride and an alcohol, whereas the present

claims use water and alcohol, acetone, or a mixture thereof. Accordingly, the Examiner submits that Ishibashi et al. discloses alcohol and acetone as suitable solvents for applying a coating solution to a core particle; Lynenskjold et al. discloses the use of organic solvents such as ethanol and acetone, with methylene chloride being possible but not preferred; and Nara et al. discloses the use of water and its mixture with an organic solvent as the coating composition solvent. Accordingly, the Examiner asserts that one skilled in the art would immediately see the benefit of using a coating solution that omits methylene chloride, such as a coating solution comprising water, a water-soluble polymer, and a solvent selected from an alcohol, acetone, and mixtures thereof.

C. Rejection of claim 7 under 35 U.S.C. § 103(a)

Whether the identified claim is unpatentable under 35 U.S.C. § 103(a) as being unpatentable over Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al. in view of Vladyka et al. (U.S. Patent No. 6,497,905). The Examiner acknowledges that Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al. do not teach the amorphous form of an azole antifungal agent as recited in present claim 7. However, the Examiner asserts that Vladyka et al. teach that azole antifungal agents, such as ketoconazole and itraconazole, have very low solubility in aqueous media and will benefit from conversion to the amorphous state. Accordingly, the Examiner asserts one skilled in the art would reasonably expect that an azole antifungal agent in its amorphous state will exhibit increased solubility per Vladyka et al. in the aqueous coating solutions as motivated and suggested by Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al.

8. Argument

A. Rejection of claim 23 under 35 U.S.C. §§ 102(b) or 103(a)

The Examiner rejected claim 23 under 35 U.S.C. §§ 102(b) or 103(a) as being anticipated by, or in the alternative, obvious over Gilis et al. (WO 00/03697).

Appellants respectfully submit that the rejection of the identified claim under 35 U.S.C. §§ 102(b) or 103(a) over Gilis et al. is improper and should be reversed.

The test for anticipation is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP § 2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ... it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of

what, in some sense, is already known." Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

It is submitted that a *prima facie* case of both anticipation and obviousness has not been established because the Gilis et al. reference fails to teach or suggest all of the limitations of the claims as required by *Verdegaal Bros. v. Union Oil Co. of California* and *In re Wilson*, respectively.

i. The presently pending claim

Present pending claim 23 recites a "pharmaceutically acceptable particle produced by the process of claim 1." Claim 1, in turn, recites a "method of manufacturing a water-insoluble azole antifungal active agent–oral dosage form, said method comprising the steps of: providing a single phase working solution comprising a water-insoluble azole antifungal active agent, water, a water-soluble polymer and a solvent, said solvent selected from the group consisting of alcohol, acetone, and mixtures thereof; providing core particles formed from a pharmaceutically acceptable material; combining said working solution with said particles to produce water-insoluble azole antifungal active agent-coated particles; drying said water-insoluble azole antifungal active agent-coated particles; and forming said dried particles into an oral dosage form; wherein said working solution is essentially free of methylene chloride,

and said oral dosage form is essentially free of methylene chloride."

Accordingly, since the working solution in claim 1 is "essentially free of methylene chloride," the particle of claim 23 produced by the process of claim 1 clearly does not contain any methylene chloride. As shown at page 3, lines 24-31 of the instant specification, by being "essentially free" of methylene chloride, the particle of claim 23 can contain less than 200, 100, 50, 20, or even 10 ppm methylene chloride.

ii. The teachings of the cited art

In contrast, the Gilis et al. reference teaches pellets having a core coated with an antifungal and a polymer. The pharmaceutical dosage form disclosed in the Gilis et al. reference is prepared using a suitable solvent system comprising a mixture of dichloromethane (i.e., methylene chloride) and an alcohol. The Gilis et al. reference specifically teaches that the solvent mixture should comprise at least 50% by weight of dichloromethane (see p. 9, lines 17-20).

Methylene chloride is a toxic industrial solvent used, for example, as a paint stripper. Among other things, it is a probable carcinogen, a neurotoxin, potentially exacerbates liver disease, and can exacerbate heart disease. Accordingly, reduction of methylene chloride intake for all people is desirable, particularly for people at risk due to age of development (e.g., children), people at risk due to other medical conditions (e.g., heart or liver disease), and/or people at risk due to exposure to methylene chloride from other sources (e.g., on the job, or in their work environment). The current recommended limit for methylene chloride in pharmaceutical products is 600 ppm (*see* Gilis et al. at page 2, lines 26-32).

While the Gilis et al. reference teaches the desirability of removing the methylene chloride present in the disclosed product, it does so not by removing methylene chloride from the disclosed process entirely, but instead by microwave drying the disclosed product after manufacture. Accordingly, methylene chloride is still an essential element of Gilis et al.'s provided manufacturing process. At least some residual methylene chloride, then, will inherently remain in the product produced by the Gilis et al. process. In fact, Gilis et al. does not provide any solution that would result in the reduction of methylene chloride to the extent taught by Appellants, and does not provide a reasonable expectation that it can be modified to eliminate methylene chloride in the final product.

In complete contrast, since the present methods require a working solution that is essentially free of methylene chloride, there is no residual methylene chloride that can be present in the resultant particle products. The lowest level of methylene chloride in the Gilis et al. product, as noted by the Examiner, is <250 ppm. However, using the microwave drying process disclosed by Gilis et al. could not achieve greater reductions in methylene chloride levels (such as the "essentially free" level required by the present claims, as described above) without burning or degrading the product itself. The microwave drying/heating process disclosed by Gilis et al., then, cannot achieve the reduced levels of methylene chloride in the final product that is achieved by Appellants' presently claimed process. Accordingly, the Gilis et al. reference does not and cannot disclose a product that is "essentially free of methylene chloride," as required by the presently pending claim.

Accordingly, for the reasons set forth above, the cited Gilis et al. reference does not teach each and every element of the presently pending claim as required by *Verdegaal Bros. v. Union Oil Co. of California* and *In re Wilson*. Accordingly, it is respectfully submitted that the product described in presently pending claim 23 is novel and unobvious over the Gilis et al. reference. Accordingly, Appellants respectfully request reversal of the Examiner's decision to reject presently pending claim 23 and that this rejection be withdrawn.

B. Rejection of claims 1-6, 15-16, 18-20, 22-23, and 42 under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-6, 15-16, 18-20, 22-23, and 43 under 35 U.S.C. § 103(a) as being unpatentable over Gilis et al. and Ishibashi et al. (U.S. Patent Application Publication No. 2003/0012815) in view of Lynenskjold et al. (U.S. Patent Application Publication No. 2003/0211168) and Nara et al. (U.S. Patent No. 6,245,351).

Appellants respectfully submit that the rejection of the identified claims under 35 U.S.C. § 103(a) over Gilis et al. and Ishibashi et al. in view of Lynenskjold et al. and Nara et al. is improper and should be reversed.

The test for obviousness is as described above in Section 8.A., the arguments of which are hereby incorporated by reference in their entirety.

i. The presently pending claims

The presently pending claims as exemplified by currently pending independent claim 1 are directed to a "method of manufacturing a water-insoluble azole antifungal

active agent-oral dosage form, said method comprising the steps of: providing a single phase working solution comprising a water-insoluble azole antifungal active agent, water, a water-soluble polymer and a solvent, said solvent selected from the group consisting of alcohol, acetone, and mixtures thereof; providing core particles formed from a pharmaceutically acceptable material; combining said working solution with said particles to produce water-insoluble azole antifungal active agent-coated particles; drying said water-insoluble azole antifungal active agent-coated particles; and forming said dried particles into an oral dosage form; wherein said working solution is essentially free of methylene chloride, and said oral dosage form is essentially free of methylene chloride."

ii. The Teachings of the Gilis et al. reference (WO 00/03697)

In contrast, the Gilis et al. reference teaches pellets having a core coated with an antifungal and a polymer. The pharmaceutical dosage form disclosed in the Gilis et al. reference is prepared using a suitable solvent system comprising a mixture of dichloromethane and an alcohol. The Gilis et al. reference specifically teaches that the solvent mixture should comprise at least 50% by weight of dichloromethane (see p. 9, lines 17-20). Further, the Gilis et al. reference does not disclose a working solution containing both the drug and water, as required by the present claims.

iii. The Teachings of the Ishibashi et al. reference (U.S. Patent Application No. 2003/0012815)

The Ishibashi et al. reference discloses a sustained release formulation prepared by spray-coating a solution containing a hydrophobic organic substance-water-soluble

polymer mixture onto a drug-containing core substance, followed by spray-coating a different hydrophobic organic compound-water-soluble polymer mixture onto the resulting coating layer. The Ishibashi et al. reference teaches compositions formed by spraying a polymeric layer on top of a drug-containing core. This is different from the presently claimed process, which requires both the drug and the polymer in the same layer.

iv. The Teachings of the Lynenskjold et al. reference (U.S. Patent Application No. 2003/0211168)

The Lynenskjold et al. reference teaches the production of spray-dried coated particles comprising an inert particulate carrier, a cellulosic binder, an active substance, and water. Lynenskjold et al. teach that the use of aqueous dispersions or solutions are preferred for the coating composition but alkanols (ethanol), ketones (acetone), and chlorinated hydrocarbons (methylene chloride) may also be used. None of the examples provided in the Lynenskjold et al. reference disclose the use of any of these solvents with water. The disclosed process of producing coated particles is different from the presently claimed process, which requires a water-insoluble azole antifungal, a water-soluble polymer, water, and a solvent in the same working solution.

v. The Teachings of the Nara et al. reference (U.S. Patent No. 6,245,351)

The Nara et al. reference teaches a drug core coated with a composition comprising a water-insoluble substance, a swellable polymer, and, optionally, a hydrophilic substance dissolved or dispersed in a solvent where the solvent can be water, an organic solvent, or mixtures thereof. The organic solvent can be ethyl alcohol

or acetone. This is different from the presently claimed process, which requires both the drug and the polymer in the same layer.

vi. The Combination of References Does Not Show All the Elements of the Pending Claims in One Working Solution, and Thus Cannot Render These Claims Obvious

The presently pending claims are distinguishable from the cited references. None of the references, taken alone or in combination, contain all the elements of the presently pending claims in the same working solution, and thus cannot render these claims obvious. In particular, present independent claim 1 recites a single phase working solution comprising a water-insoluble azole antifungal active agent, water, a water-soluble polymer and a solvent, said solvent selected from the group consisting of alcohol, acetone and mixtures thereof, wherein said working solution is essentially free of methylene chloride, and said oral dosage form is essentially free of methylene chloride (Emphasis added).

In contrast, Gilis et al. and Ishibashi et al. both disclose dichloromethane as a suitable solvent. Accordingly, the solvent system recited in the present application is different from the solvent systems disclosed in the Gilis et al. and Ishibashi et al. references. The Gilis et al. reference discloses that dichloromethane levels in the final product should be limited; however, the reference also teaches away from the present claims by including 50% dichloromethane in the solvent system. Nothing in the Gilis et al. reference suggests a solvent system that does not include dichloromethane. Further, the Gilis et al. reference teaches that azole antifungal compounds are sparingly

soluble in water, and that other non-aqueous based systems must be used in order to solubilize the compounds (see p. 1, lines 9-34).

The Ishibashi et al. reference teaches that solvents should be selected according to the hydrophobic organic compound and water soluble polymer used. However, the Ishibashi et al. reference discloses the use of dichloromethane and carbon tetrachloride as suitable solvents, which are specifically excluded from the presently pending claims. Further, the Ishibashi et al. reference does not state how to reduce or eliminate the levels of dichloromethane to the extent taught by the present application. Therefore, the Ishibashi et al. reference does not remedy the deficiencies of the Gilis et al. reference.

Regarding the Lynenskjold et al. reference, this reference teaches the production of spray-dried coated particles comprising an inert particulate carrier, a cellulosic binder, an active substance, and water, while the presently pending independent claim 1 teaches a working solution comprising a water-insoluble azole antifungal active agent, water, a water soluble polymer and a solvent, said solvent selected from the group consisting of alcohol, acetone, and mixtures thereof. Lynenskjold et al. disclose that organic solvents can be used in the preparation of the composition but an aqueous solution or dispersion is preferred. The organic solvent can be methylene chloride, ethanol or acetone. Lynenskjold et al. does not teach or suggest the combination of water and an organic solvent along with the water soluble polymer. The examples in the reference do not include organic solvents along with water in the production of the particulate compositions. Therefore, the Lynenskjold et al. reference does not remedy the deficiencies of Gilis et al. or Ishibashi et al. as it shows a different solvent system

that does not contain all the elements in the same working solution as required by the presently pending claims.

The Nara et al. reference teaches a drug core coated with a coating composition comprising a water-insoluble substance, a swellable polymer, and, optionally, hydrophilic substances dissolved or dispersed in a solvent. While the solvent can be water, an organic solvent, or mixtures thereof, this solvent system does not include a water-insoluble azole antifungal active agent or any other active agent. The presently pending claims require that the solvent system and the drug be in the same working solution and, in turn, be present in the same coating layer on the core particle. Therefore, Nara et al. does not remedy the deficiencies of Gilis et al. or Ishibashi et al. or Lynenskjold et al. as it does not show a coating solution that contains an active agent in the working solution as required by the presently pending claims.

None of the cited references disclose a working solution containing the drug, water-soluble polymer, organic solvent, and water, wherein the working solution is essentially free of methylene chloride as required by the present claims. Therefore, it would have been unexpected for a person having ordinary skill in the art to use water and an organic solvent to process a water-insoluble drug. Further, Ishibashi et al. and Nara et al. both teach compositions formed by spraying a polymeric layer on top of a core substance containing a drug. In contrast, the presently claimed process requires both the drug and the polymer to be contained in the same layer.

Accordingly, the Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al. references, taken alone or in combination, do not show all of the elements of the

presently pending claims in the same working solution, and thus cannot render these claims obvious. Thus, all of the limitations of the presently pending claims are not shown by the combination of the cited references, as required by *In re Wilson*.

vii. No Motivation Exists to Combine the References and Thus Cannot Render These Claims Obvious

The Examiner asserts in the Office Action that Appellant is attacking the references individually by pointing out how specific claim limitations are not met by the individual references. However, as noted in this response, the references, taken alone or in combination, do not teach each and every element of the presently claimed subject matter. In addition, the Examiner has established no motivation to combine the references.

With regard to motivation to combine references, **MPEP 2143** discusses the requirements of a *prima facie* case of obviousness. First, there must be some suggestion or motivation to combine the reference teachings or to modify the reference, and second, there must be a reasonable expectation of success. Finally, the prior art reference or references when properly combined must teach or suggest all the claim limitations.

Regarding motivation to modify properly combined references, **MPEP 2143.01** states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), the Federal Circuit rejected Alphapharm's argument that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound most promising to modify in order to improve its antidiabetic activity and thus potentially arrive at the claimed pioglitazone. The Federal Circuit considered three references in reaching its determination, namely Takeda's '200 patent; Sodha II; and Takeda's '779 patent. The Federal Circuit found that Sodha II taught away from compound b and that any suggestion in the '779 patent to select compound b was essentially negated by the disclosure of Sodha II in view of the more exhaustive and reliable scientific analysis presented by Sodha II and the teaching away. Accordingly, the Federal Circuit accorded more weight to the Sodha II reference.

It is submitted that a *prima facie* case of obviousness has not been established because the skilled artisan would have no motivation to modify Gilis et al. or Ishibashi et al. to incorporate the solvent system of Lynenskjold et al. or the solvent coating system of Nara et al.

Gilis et al. teaches a bead core coated with a very sparingly water-soluble drug and a hydrophilic polymer. The Ishibashi et al. reference teaches a drug core coated with a coating layer of a hydrophobic substance and a water-soluble polymer. Neither reference includes water in their respective coating layers. Lynenskjold et al. and Nara et al. each teach a coating composition that contains water. One of ordinary skill in the art would not substitute the water-containing solvent systems of Lynenskjold et al. or Nara et al. with those of Gilis et al. or Ishibashi et al. Gilis et al. and Ishibashi et al.

provide no motivation to provide water in their coating systems for a very sparingly water-soluble active agent and hydrophobic substance, respectively. Therefore, one of ordinary skill in the art would not look to Lynenskjold et al. or Nara et al. for a solvent system containing water to dissolve a very sparingly water-soluble active agent or a hydrophobic substance.

In further support of this argument, Appellants respectfully submit that the process of the presently pending claims provides particles that have an increased solubility under dissolution conditions at pH 5.0, resulting in enhanced bioavailability of the active ingredient. Table 5 on page 24 of the present specification shows that the azole antifungal composition had a dissolution rate increase by 129% over the dissolution profile of the commercial product SPORANOX® under fasted conditions. The table further shows that the dissolution rate increased by 74% over the commercial product under fed conditions.

In the final Official Action dated December 1, 2008, the Examiner found Appellants' unexpectedly superior results unpersuasive. In particular, the Examiner stated that "Applicants have not described exactly how the itraconazole particles tested in the example at page 24 were prepared (solvent system, water-soluble polymer, etc.) nor how the commercial SPORANOX® particles were prepared." In addition, the Examiner states that the itraconazole particles tested by Appellants are not commensurate in scope with the patent protection being sought. *See* page 7 of the December 1, 2008 Official Action.

In response to the Examiner's comments regarding the unexpectedly superior results, Appellants point to the parent application of the presently pending application, U.S. Patent Application No. 09/933,032, U.S. Patent No. 6,663,897 (hereinafter "the '897 patent"), to provide the requested information regarding the process by which the itraconazole particles and SPORANOX® particles were produced. In addition, the '897 patent provides further dissolution test results to show the increased dissolution profile for the itraconazole particles of the presently pending application.

The itraconazole particulate compositions discussed in the present application are consistent with those described and disclosed at col. 6, lines 1-67, of the specification of the '897 patent, as per the below listing. The below listing present in the '897 patent includes the percentages for each ingredient of the total composition and the specific quantity of each of the individual ingredients present therein.

Itraconazole and Hydrochloric Acid ratio is 1:1.6 Moles

Name of Ingredient	Percent	Quantity
Microcrystalline Cellulose Spheres (Celpheres)[1]	36.28	1,500 g
Micronized Itraconazole	18.86	780 g
Hydroxy Propyl Methyl Cellulose 5 cps	42.45	1,755 g
Titanium Dioxide USP	0.85	35.1 g
Hydrochloric Acid 37% NF/EP[2]	1.56	174.5 g
Alcohol SD3A Anhydrous[3]	0.0	28,070 g
Purified Water USP/EP[3]	0.0	3,264 g
Total	100.0	4,134.66 g

[1]CP 507 grade Celpheres ® are used
[2]Supplied as 37% Hydrochloric Acid and contributes 64.56 g of total solids
[3]Removed in the process

The itraconazole particulate composition was prepared according to the following steps:

a. A 19.22 kg portion of SD3A alcohol was added to a stainless steel container. The hydroxypropyl methyl cellulose was added under stirring. When it forms a uniform suspension, the purified water was added under stirring. The stirring was continued until a translucent solution was formed. At the end of stirring, titanium dioxide was added and stirring continued for another ten minutes until a uniform suspension was formed.

b. Next, a 6.85 kg portion of SD3A alcohol was combined with the hydrochloric acid and stirred for ten minutes. To this solution, the itraconazole was added under stirring and the stirring continued for an additional fifteen minutes.

c. Next, the itraconazole solution was added to the hydroxypropyl methyl cellulose solution under stirring and stirring continued for 20 minutes. After stirring was completed the solution was homogenized for 2 minutes. The pH of the solution is then checked and a 2.0 kg portion of SD3A alcohol

was added under impeller stirring. At this stage the weight of the solution is checked and adjusted accordingly with additional quantities of alcohol.

d. A Glatt GPCG-5 fluidized bed coater equipped with a Wurster spray insert is used for coating of the particles. Note that powder generation (spray drying) should be avoided and the filter bag placed properly to avoid losses. The spray rate is gradually increased from a starting rate of 15 grams to a final rate of 30 to 35 grams per minute towards the end of the process. Loading is performed at a temperature of 34-42° C. The coated particles are then dried for approximately 10-12 hours in a tray dryer at 45-50° C.

e. The coated particles described above are then used to fill a size 0, CAPSUGEL™ elongated hard gelatin capsule to provide a finished oral dosage having the ingredient weights and proportions as set forth below.

The SPORANOX® particles, which serve as the basis for comparison for the dissolution tests disclosed in the '897 patent, as well as the presently pending application, are available commercially. SPORANOX® is the subject of a New Drug Application (ND 20-083) which was approved on September 11, 1992 as a drug product. SPORANOX® is protected by U.S. Patent No. 5,633,015 (hereinafter "the '015 patent"). The '015 patent is assigned to Janssen Pharmaceutica N.V. The process by which the SPORANOX® particles are prepared is recited in an example of the '015 patent beginning at col. 4, line 63, and continuing through col. 6, line 15. The SPORANOX® particulate composition was prepared according to the following steps:

a) Itraconazole Spraying Solution

An inox vessel was charged with methylene chloride (375kg) and denatured ethanol (250 kg) through a filter *(5μ)*. Itraconazole (21.74 kg) and hydroxypropyl methylcellulose 2910 5 mPa.s (32.61 kg) was added while stirring. Stirring was continued until complete dissolution was obtained (A suitable saperconazole spraying solution was obtained using

an identical procedure).

b) Seal-Coating Spraying Solution

An inox vessel was charged with methylene chloride (21.13 kg) and polyethylene glycol 20000 (Macrogol 20000) (3.913 kg) while stirring. Denatured ethanol (14.09 kg) was added and the solution was stirred until homogeneous.

c) Drug Coating Process

A fluidized-bed granulator (Glatt, typeWSG 30) equipped with a 18 inch Wurster (bottom spray) insert was loaded with 25-30 mesh (600-700 μm) sugar spheres (41.74 kg). The spheres were warmed with dry air of 50°-55° C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 50% of its maximum in the beginning, increasing up to 60% at the end of the spraying process. The previously prepared itraconazole spraying solution was then sprayed on the spheres moving in the apparatus. The solution was sprayed at an initial delivery rate of about 600 to 700 $g.min^{-1}$ at an atomizing air pressure of about 3.5 kg/cm^2 (0.343 MPa). After delivery of about 30% of the spraying solution, the delivery rate was increased to 700-800 g/min.

When the spraying process was completed, the coated spheres were dried by further supplying dry air of 50°-55° C. for about 10 minutes. The coated spheres were then allowed to cool in the apparatus by supplying dry air of 20°-25° C. for about 10 to 20 minutes. The apparatus was emptied and the coated spheres were collected.

d) In-Between Drying

In order to minimize residual solvent levels the coated spheres were then subjected to a drying step. The coated spheres were introduced in a vacuum tumbler-drier and dried for at least 24 hours, preferably about 36 hours, at a temperature of about 80° C. at a pressure of about 200-300 mbar (20-30 kPa). The tumbler-drier was operated at its minimal rotation speed (2 to 3 rpm). The dried coated spheres were sieved with a sieve (Sweco S24C; sieve mesh width 1.14 mm).

e) Seal-Coating Process

The dried coated spheres were introduced again in the fluidized-bed granulator equipped with the Wurster insert and warmed with dry air of

50°-55° C. The previously prepared seal-coating spraying solution was then sprayed on the coated spheres moving in the apparatus. The solution was sprayed at an delivery rate of about 400 to 500 $g.min^{-1}$, at an atomizing air pressure of about 2.5 bar (0.25 MPa). When the spraying process was completed, the beads were dried by further supplying dry air of 50°-55° C. for 10 min. The coated spheres were then allowed to cool in the apparatus by supplying dry air of 20°-25° C. for about 5 to 15 minutes. The beads were removed from the apparatus and stored in suitable containers.

f) Capsule Filling

The drug coated beads were filled into hard-gelatin capsules (size 0) using standard automatic capsule filling machines (e.g. Model GPK.-1500, H60ffliger and Karg. 5 Germany). In order to obtain capsules with good weight distribution, capsule filling speed was reduced to about 75-85% of the maximum speed. Each capsule received approximately 460 mg beads, equivalent to about 100 mg itraconazole. Using the process parameters described above, itraconazole 100 mg hard-gelatin capsules were obtained which met all the requirements, in particular the dissolution specifications.

The itraconazole particles prepared by the process described in the '897 patent and described above, and the commercially available SPORANOX® particles were subjected to the same dissolution tests. The first dissolution test, conducted at a pH of 1.2, is described in Example 2 of the '897 patent at col. 7, line 1, through col. 8, line 40. The results of the dissolution test for each type of particles are set forth below.

Dissolution Test Results in Simulated Gastric Fluid (pH 1.2)

Product Details		Minimum	Maximum	Aver-age	Std. Dev.	% RSD
Example 1 Capsules	% Dissolved in 30 minutes	83.3	91.0	87.0	3.7	4.3
	% Dissolved in 60 minutes	94.9	102.6	97.7	3.0	3.1
	% Dissolved in 720 minutes	102.0	103.1	102.7	0.5	0.5
Sporanox Capsules	% Dissolved in 30 minutes	47.7	79.2	59.4	—	—
	% Dissolved in 60 minutes	71.2	98.7	82.0	—	—
	% Dissolved in 720 minutes	86.4	102.8	96.6	—	—

The itraconazole particles prepared by the process described in the '897 patent and described above, and the commercially available SPORANOX® particles were also subjected to a second dissolution test, wherein the test was conducted at a pH of 5.0. This dissolution test is described in Example 3 of the '897 patent at col. 8, line 41, though col. 9, line 18. The results of the dissolution test at a pH of 5.0 for each type of particles are set forth below.

Dissolution Data in pH 5.0 Phosphate Buffer.

Product Details		Minimum	Maximum	Aver-age	Std. Dev.	% RSD
Example 1 Capsules	% Dissolved in 30 minutes	28.4	40.5	33.7	5.0	14.8
	% Dissolved in 60 minutes	56.1	64.1	61.0	3.6	5.9
	% Dissolved in 720 minutes	51.3	53.2	52.3	0.8	1.5
Sporanox Capsules	% Dissolved in 30 minutes	2.7	2.8	2.7	—	—
	% Dissolved in 60 minutes	5.7	6.8	6.3	—	—
	% Dissolved in 720 minutes	4.9	5.3	5.1	—	—

The dissolution tests at pH 1.2 and 5.0 referenced in the '897 patent show that the water-insoluble azole antifungal particles prepared in Example 1 of the '897 patent display a significantly more rapid dissolution profile than the commercially available SPORANOX® particles. This finding indicates that the particles produced by the process of the presently pending application dissolve more rapidly than the SPORANOX® particles under pH conditions that represent both fed and fasted conditions in a subject receiving such treatment.

The increased dissolution profile of the particles produced by the process of the presently pending claims leads to an enhanced bioavailability of the active ingredient of the particles. This enhanced bioavailability is shown at Table 5 on page 24 of the presently pending application.

Further, the Supreme Court in *KSR* reiterated the framework for determining obviousness that was stated in *Graham v. John Deere Co.* 383 U.S. 1, 148 USPQ 459 (1966). The four factual inquiries that were recited in *Graham* are as follows: (1) Determining the scope and contents of the prior art; (2) Ascertaining the differences between the prior art and the claims in issue; (3) Resolving the level of ordinary skill in the pertinent art; and (4) Evaluating evidence of secondary considerations, such as unexpected results. Id. As stated in **MPEP 2141**, secondary considerations such as unexpected results must be considered in every case in which they are present.

Accordingly, since the Examiner insists on maintaining that a prima facie case of obviousness has been established against the presently pending claims, Appellants respectfully submit that they have successfully rebutted this finding of obviousness by demonstrating unexpectedly superior results for the claimed subject matter. In this regard, Appellants respectfully point to Table 5 on page 24 of the presently pending application and the dissolution test results of the '897 patent, showing an unexpectedly superior dissolution profile over the commercial product. Accordingly, the presently claimed subject matter is not obvious in view of the references cited by the Examiner.

In view of the foregoing, it is submitted that nothing in Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al., taken alone or together, renders the presently pending claims obvious within the meaning of 35 USC § 103. Accordingly, Appellants respectfully request reversal of the Examiner's decision to reject presently pending claims 1-6, 15-16, 18-20, 22-23, and 42 and that this rejection be withdrawn.

C. Rejection of claim 7 under 35 U.S.C. § 103(a)

The Examiner rejected claim 7 under 35 U.S.C. § 103(a) as being unpatentable over Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al. in view of Vladyka et al. (U.S. Patent No. 6,497,905).

Appellants respectfully submit that the rejection of the identified claim under 35 U.S.C. § 103(a) over Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al. in view of Vladyka et al. is improper and should be reversed.

The test for obviousness, the scope of the presently pending claims, and the teachings of Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al. are discussed above in Sections 8.A. and 8.B., the contents of which are hereby incorporated by reference in their entirety. None of the cited references teach the active agent in an amorphous form.

The Vladyka et al. reference teaches a solid solution of an azole compound in an amorphous state dissolved in a molten solution of a hydrophobic vehicle, a stabilizing agent, a disintegrant, and optionally a binder. This composition is formulated by melting the hydrophobic vehicle at a temperature above its melting point but below that of the azole compound and dissolving the azole compound in the hydrophobic vehicle, followed by a granulation and cooling step. In contrast, the presently pending claims require a working solution comprising a water-insoluble azole antifungal, a water-soluble polymer, water and a solvent that is coated onto a carrier particle. The process of the presently pending claims is completely different from the process taught by Vladyka et al. In addition, the process of Vladyka et al. is completely different from the references

whose deficiencies it is meant to cure. None of the Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al. references teaches a melt granulation process to form a solid solution, as required by Vladyka et al.

Vladyka et al. does not cure the deficiencies of Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al. as it does not teach that an amorphous drug can be contained in a solution of water-soluble polymer, water and an organic solvent to be sprayed onto a core particle. In addition, there is no motivation to combine the teachings of Vladyka et al. with those of Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al. because one of ordinary skill in the art would not look to a reference teaching granulation of a melted solid solution to substitute components with a solution containing a water soluble polymer, water and an organic solvent to be coated onto a particle.

In view of the foregoing, it is submitted that nothing in Gilis et al., Ishibashi et al., Lynenskjold et al., Nara et al., and Vladyka et al., taken alone or together, renders the presently pending claims obvious within the meaning of 35 USC § 103. Accordingly, Appellants respectfully request reversal of the Examiner's decision to reject presently pending claim 7 and that this rejection be withdrawn.

For the foregoing reasons, Appellants respectfully submit that the Examiner's rejection of presently pending claims 1-7, 15-20, 22-23, and 42 was erroneous. Accordingly, Appellants respectfully request reversal of the Examiner's decision and the allowance of the pending claims.

The Commissioner is authorized to charge Deposit Account No. 14-0112 for any

additional charges in connection with this appeal. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such extension is requested and the fee should also be charged to our Deposit Account No. 14-0112.

The Examiner is welcomed to contact the undersigned attorney if such contact would be helpful in the further prosecution of this case.

Respectfully submitted,

THE NATH LAW GROUP

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9. Claims Appendix

1. (Previously presented) A method of manufacturing a water-insoluble azole antifungal active agent-oral dosage form, said method comprising the steps of:

providing a single phase working solution comprising a water-insoluble azole antifungal active agent, water, a water-soluble polymer and a solvent, said solvent selected from the group consisting of alcohol, acetone, and mixtures thereof;

providing core particles formed from a pharmaceutically acceptable material;

combining said working solution with said particles to produce water-insoluble azole antifungal active agent-coated particles;

drying said water-insoluble azole antifungal active agent-coated particles; and

forming said dried particles into an oral dosage form;

wherein said working solution is essentially free of methylene chloride, and said oral dosage form is essentially free of methylene chloride.

2. (Previously presented) The method of claim 1, further comprising the step of adjusting the pH of said working solution to solubilize said water-insoluble azole antifungal active agent prior to said providing step.

3. (Previously presented) The method of claim 1, wherein said working solution further comprises a surfactant.

4. (Previously presented) The method according to claim 1, wherein said single phase working solution has a viscosity of from 10 – 2000 mPa.s during said combining step.

5. (Previously presented) The method according to claim 1, wherein the ratio of water-insoluble azole antifungal active agent–to water-soluble polymer in said working solution is from 1:0.5 to 1:20 on a weight: weight basis.

6. (Previously presented) The method according to claim 1, wherein the ratio of solvent to water in said working solution is from 50:50 to 95:5 on a weight: weight basis.

7. (Previously presented) The method according to claim 1, wherein said water-insoluble azole antifungal active agent comprises active agent in amorphous form.

8. (Canceled)

9. (Withdrawn) The method of claim 1, wherein said active agent is selected from the group consisting of saquinavir, cyclosporine and paclitaxel.

10. (Withdrawn) The method of claim 1, wherein said active agent is saquinavir.

11. (Withdrawn) The method of claim 1, wherein said active agent is cyclosporine.

12. (Withdrawn) The method of claim 1, wherein said active agent is paclitaxel.

13. (Withdrawn) The method of claim 1, wherein said active agent is subject to the proviso that sparingly water soluble antifungal agents are excluded there from.

14. (Canceled)

15. (Previously presented) The method according to claim 1, wherein said alcohol is selected from the group consisting of methanol, ethanol, propanol, butanol, and mixtures thereof.

16. (Previously presented) The method according to claim 1, wherein said water-soluble polymer is selected from the group consisting of hydroxypropyl methylcellulose, methacrylate, hydroxypropylcellulose, polyvinylpyrrolidones, dextrins and maltodextrins.

17. (Previously presented) The method according to claim 3, wherein said surfactant is selected from the group consisting of Sodium Lauryl Sulfate; Polysorbate 20,

40, 60, 80; Polyoxyethylene glycolated natural or hydrogenated vegetable oils such as polyoxyethylene glycolated natural or hydrogenated castor oils (Cremophor ®), Poloxamer, Polyoxyethylen 50 Stearate, Propylene Glycol Monostearate, Sorbitan Monolaurate, Sorbitan Monooleate, Sorbitan Monopalmitate, and Sorbitan Monostearate.

18. (Previously presented) The method according to claim 1, wherein said core particles comprise microcrystalline cellulose spheres.

19. (Previously presented) The method according to claim 1, wherein said core particles comprise mannitol spheres.

20. (Previously presented) The method according to claim 1, wherein said core particles are from 100 to 1000 micrometers in diameter.

21. (Canceled)

22. (Previously presented) The method of claim 1, wherein said drying step is followed by the step of coating said spheres with an external coating.

23. (Previously presented) A pharmaceutically acceptable particle produced by the process of claim 1.

24. (Withdrawn) The particle of claim 23, wherein said active agent is selected from the group consisting of saquinavir, cyclosporine and paclitaxel.

25. (Withdrawn) The particle of claim 23, wherein said active agent is saquinavir.

26. (Withdrawn) The particle of claim 23, wherein said active agent is cyclosporine.

27. (Withdrawn) The particle of claim 23, wherein said active agent is paclitaxel.

28. (Withdrawn) A pharmaceutically acceptable particle comprising:
a central rounded or spherical core comprised of a core material; and a coating film formed on said core, said coating film comprising a water-soluble polymer and active agent; with said particle comprising, by weight, from 5 to 40 percent active agent; from 10 to 80 percent particle core material; and from 10 to 80 percent water-soluble polymer;
and with said particle containing less than 200 ppm methylene chloride.

29. (Withdrawn) The particle according to claim 28, wherein said active agent comprises active agent in amorphous form.

30. (Withdrawn) The particle according to claim 28, wherein said active agent is selected from the group consisting of protease inhibitors, proton pump inhibitors,

oligopeptides, statins, antibiotics, antifungals and antineoplastics.

31. (Withdrawn) The particle according to claim 28, wherein said core material comprises microcrystalline cellulose.

32. (Withdrawn) The particle according to claim 28, wherein said water soluble polymer is selected from the group consisting of hydroxypropyl methylcellulose, polymethacrylate, hydroxypropylcellulose, polyvinylpyrrolidones, dextrins and maltodextrins.

33. (Withdrawn) The particle according to claim 28, wherein said particle further comprises an external coating formed on said coating film.

34. (Withdrawn) An active agent oral dosage form comprising a pharmaceutically effective amount of particles according to claim 28.

35. (Withdrawn) The dosage form according to claim 34, wherein said dosage form contains from 5 to 500 milligrams of active agent.

36. (Withdrawn) The dosage form according to claim 34, wherein said dosage form is a hard-gelatin capsule.

37. (Withdrawn) The dosage form according to claim 34, wherein said dosage form is a tablet.

38. (Withdrawn) The dosage form according to claim 34, wherein said dosage form is free of lipid or oil solvent.

39. (Withdrawn) A method of treating a disorder in a subject in need thereof, comprising orally administering to said subject an oral dosage form according to claim 34 in a pharmaceutically acceptable amount.

40. (Withdrawn) The method according to claim 39, wherein said oral dosage form is administered to said subject under fed conditions.

41. (Withdrawn) A method according to claim 39, wherein said oral dosage form is administered to said subject under fasted conditions.

42. (Previously presented) The method according to claim 1, wherein the water-insoluble azole antifungal active agent is ketoconazole.

10. Evidence Appendix

None

11. Related Proceedings Appendix

None